MicroRNAs' Impact on Sleep-Related Epilepsy

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MicroRNAs are a family of single-stranded, non-coding, endogenous regulatory molecules formed from double-stranded precursors. They are typically composed of 21–23 nucleotides, and their main role involves post-transcriptional downregulation of expression of numerous genes. Learning more about the role of microRNAs in the pathogenesis of sleep disorder epilepsy may result in its use as a biomarker in these disorders and application in therapy.

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1. Sleep-Related Seizures—Selected Epilepsy Syndromes

The sleep–wake cycle has an effect on epilepsy. Sleep-related hypermotor epilepsy (SHE) and Panayiotopoulos syndrome (PS) are two of the most frequently implicated epilepsies occurring during the sleep state [1]. Generalized epilepsy, such as juvenile myoclonic epilepsy (JME), is most often associated with awakening.

SHE occurs during the non-rapid eye movement (NREM) stage of sleep. The hypothesis proposed by Zupcic et al. [2] is that seizures and the development of epileptogenesis in SHE are a consequence of cholinergic dysfunction and decreased levels of microRNA-211, as opposed to NREM parasomnias, where there is a stable level of microRNA-211, preventing epileptogenesis despite the cholinergic system dysfunction.

BECTS is the most common childhood epilepsy syndrome, in which seizures occur almost exclusively in sleep at the transition between rapid eye movement (REM) and non-REM cycles [3]. The clinical features include oropharyngolaryngeal symptoms (OPLS) (present in 50% of patients), speech arrest (40% of patients), unilateral facial sensorimotor symptoms (30% of patients), and hypersalivation (30% of patients). Characteristic changes in electroencephalographic recordings are centrotemporal spikes (CTS) arising independently in the right and/or left hemispheres from a normal background activity. Typical and atypical BECTS are presumed to have a shared genetic etiology. The pathogenesis of BECTS has been linked to the Elongator Complex (also called PAXNEB)—in particular, Elp 4–6 maintain translational fidelity via regulation of tRNA modifications. It has been shown that there are active genes located inside chromosomes, as exemplified by the approximately 1 Mpz region of 11p13 which contains, in addition to stretches of intergenic DNA of approximately 300 kpz, a large number of genes whose expression is regulated by ubiquitination (RCN and PAXNEB). The PAXNEB gene encodes a protein involved in elongation and is a homolog of elongation protein 4 in *Saccharomyces cerevisiae* [4]. GRIN2A gene mutations are more commonly found in the atypical form of BECTS. GRIN2A encodes the GluN2A subunit of the NMDAR. The

functional consequences of mutations in GRIN2A are altered Zn2+ binding and loss of Zn2+ inhibition, which plays a critical role in normal neuronal development, synaptic plasticity and memory [5][6][7][8][9].

Panayiotopoulos syndrome is defined as a benign, age-related epilepsy syndrome characterized by seizures with predominant autonomic symptoms and multifocal EEG changes predominantly in the occipital region. It has been hypothesized that a mutation in SCN1A, the gene encoding the α-subunit of the brain type I voltage-gated sodium channel Nav1.1, may cause susceptibility to the occurrence of PS. Voltage-isolated sodium channel Nav1.1 plays an important role in controlling neuronal excitability. MicroRNA-155 is believed to target Nav1.1 and may play a role in the seizure inhibitory effects of valproic acid. Silencing of Nav1.1 by microRNA is an important regulator of neuronal excitability in epilepsy [10].

Juvenile myoclonic epilepsy (JME) is characterized by myoclonic jerks 1–2 h after awakening. It is a heterogeneous syndrome with an autosomal dominant inheritance. Genetic analyses of families with JME have revealed mutations in numerous genes: EFHC1, ClCN2, KCNQ3, KCNMB3, GABRA1, and BRD2. Less documented for the pathogenesis of this epilepsy syndrome are mutations within KCNJ10 and CACNA1A. Seizures are sometimes provoked by fatigue, sleep deprivation, emotions, and alcohol abuse [11][12] (**Table 1**).

Table 1. Dysregulated miRNAs in the patient with sleep-related epilepsy syndromes [13][2][5][6][7][8][9].

	miRNA	Gene Type
sleep-related hypermotor epilepsy (SHE)	miRNA-211	CHRNA4, CHRNA2 CHRNB2
Panayiotopoulos syndrome	miRNA-155	SCN1A
benign partial epilepsy with centrotemporal spikes (BECTS)	miRNA-328	PAXNEB GRIN2A (atypical form)
idiopathic generalized epilepsy, including juvenile myoclonic epilepsy (JME)	miR 194-5p and miR 106b	EFHC1, ClCN2, KCNQ3, KCNMB3, GABRA1,BRD2, KCNJ10, CACNA1A

2. Sudden Unexpected Death in Epilepsy

Sudden unexpected death in epilepsy (SUDEP) is defined as “sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicological cause of death” [14][15]. SUDEP is responsible for a total of about 8–17% of the causes of death in epilepsy patients. In adults, the prevalence of SUDEP is estimated at approximately 1.2 cases per 1000 people per year [14]. The most probable, commonly known risk factors for SUDEP are early age of onset, male gender, long duration of the disease, generalized tonic-clonic seizures (GTCS), the underlying disease causing the epilepsy, polytherapy, and patient’s lack of cooperation in the treatment process. The structural brain abnormalities, abnormal neurological assessment and intellectual disability, and psychiatric comorbidities also predispose to SUDEP [16]. In addition, the risk of SUDEP increases when seizures occur during sleep and at night [14][17][18]. In 2015, Mostacci et al. found that patients with nocturnal frontal lobe epilepsy (the syndrome’s name has been

changed from autosomal dominant nocturnal frontal lobe epilepsy to sleep-related hypermotor epilepsy) did not show a higher risk of SUDEP. They suggested the need for an additional risk factor for SUDEP, possibly the occurrence of GTCS [19]. SUDEP pathomechanisms may result from arrhythmias, paroxysmal cardiomyopathy, dysfunction of the autonomic nervous system, and seizure-related respiratory failure. Nashef et al. [15] indicated the possibility of a coexisting susceptibility to sudden cardiac death—independent of or related to the epilepsy—that becomes symptomatic in the presence of uncontrolled seizures. It is extremely important that there is a group of epilepsy patients with various types of cardiac repolarization abnormalities that also occur in the interictal period. The occurrence of these changes, regardless of epileptic seizures, may be associated with gene mutations (e.g., leading to long QT syndrome and catecholaminergic polymorphic ventricular tachycardia) and mutations of the sodium channel genes SCN1A, SCN5A, potassium KCNH2, etc., which may cause the clinical picture of the disease with seizures, epilepsy, and fatal arrhythmias. Genetically conditioned shortening of the QT complex may be associated with peri-paroxysmal tachyarrhythmia and an increased risk of SUDEP. The discovery of mutations in the KCNQ1 gene in laboratory animals is associated with their predisposition to the occurrence of long QT syndrome and epileptic seizures. Because long QT is associated with an increased risk of arrhythmias, it appears to be responsible for a certain percentage of SUDEP cases as well [17][20][21].

Scorza et al. [17] suggested, that modifications to the expression pattern of circulating miRNAs may be associated with abnormal underlying cardiovascular processes and may be identified and used as SUDEP biomarkers [17]. De Matteis et al. [22] conducted a study of patients with SUDEP compared with 10 autopsies of traumatic or asphyxia deaths. They analyzed the expression profiles of several miRNAs (miR-301a-3p, miR-194–5p, miR-30b-5p, mIR-342-5p, and miR-4446-3p) from the plasma and temporal lobe and identified upregulation of miR-301a-3p in the plasma (2.3-fold) and hippocampus (3.2-fold) for SUDEP vs. controls [14][22]. Pansani et al. [23], in animal models of epilepsy, found in the group of rats with epilepsy and five GTCS increased in microRNA-21 and decreased in microRNA-320 expression compared to the group of rats without epilepsy and the group of rats with epilepsy and ten GTCS. Therefore, seizures impair cardiac function and morphology, probably through microRNA modulation [23].

A new class of specific circulating miRNAs has been identified as potential biomarkers of cardiovascular disorders, therefore there is a reasonable focus that the same molecules could also be useful in the investigation of SUDEP [17]. However, most authors believe that this potential biomarker still needs to be confirmed with additional cases.

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